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(54) Title: REMEDIES FOR ARACHIDONIC ACID-INDUCED SKIN DISEASES

(54) 発明の名称: アラキドン酸誘発皮膚疾患治療剤

(57) Abstract: Drugs for preventing and/or treating arachidonic acid-induced skin diseases which contain as the active ingredient 4-amino-2-ethoxymethyl-α,α dimethyl-1H-imidazo[4,5-c]quinoline-1-ethanol:R848 or its acid addition salt or solvate. By using these drugs, various skin diseases caused by the accelerated arachidonic acid metabolism (psoriasis, ultraviolet dermatitis, mastocytoma, basiloma, squamous cell carcinoma, etc.) can be safely and effectively treated.

(57) 要約:

４－アミノ－２－エトキシメチル－α，αジメチル－１Ｈ－イミダゾ［４，５－ｃ］キノリン－１－エタノール：Ｒ８４８、又はその酸付加塩若しくは溶媒和物を有効成分とする、アラキドン酸代謝亢進に起因する皮膚疾患の予防及び／又は治療のための薬剤。これにより、アラキドン酸代謝亢進に起因する各種皮膚疾患（乾癬、紫外線皮膚炎、肥満細胞症及び基底細胞腫、有刺細胞癌等）を安全かつ効果的に治療できる。

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明細書

アラキドン酸誘発皮膚疾患治療剤

技術分野

本発明は、皮膚疾患治療剤に関する。さらに詳しくは、乾癬、紫外線皮膚炎、肥満細胞症、基底細胞癌または有刺細胞癌などのアラキドン酸代謝亢進に起因する皮膚疾患の予防または治療剤に関する。

背景技術

アラキドン酸代謝経路により生成されるプロスタグランジン（ＰＧ）類やロイコトリエン類(ＬＴ)は、胃酸分泌や血小板凝集、種々の平滑筋収縮など生理的機能調節に係わるとともに組織の炎症を惹起する脂肪酸系の情報伝達物質（メディエーター）である。ＰＧやＬＴは生体の恒常性維持に重要であるが、一部の皮膚疾患においては、その過剰産生が疾患の主たる病因と考えられている。

このような皮膚疾患の代表例として、まず乾癬が挙げられる。乾癬は表皮細胞の良性の異常増殖と、表皮内への多形核白血球の侵入を示す慢性疾患であり、下記(1)～(4)の理由から、アラキドン酸代謝産物異常と密接に関連する疾患と考えられている。(1)乾癬皮疹部ではＰＧ、アラキドン酸、１２－ＨＥＴＥが増加する (Hammerstrom, S. et al. Proc. Nat. Acad. Sci. USA. 72, 5130-5134 (1975))、(2)ＬＴＢ４をヒト皮膚に貼布すると、乾癬皮疹部にみられる表皮内の微小膿瘍が形成される(Camp, S. et al. J. Invest. Dermatol. 82, 202-204 (1984))、(3)ＰＧの血管拡張作用とロイコトリエンＣ、ＤおよびＥ(ＬＴＣ、ＬＴＤ、ＬＴＥ)の血管透過性亢進により皮膚の発赤・浮腫反応が惹起される、(4)ロイコトリエン５，１２－ジヒドロキシ体(ＬＴＢ４)により多核白血球遊走が増強され乾癬等に特徴的な角層下、角層内膿ほうが形成される。現在、トレチナート(ビタミンＡ誘導体)、活性

型ビタミンＤ３、シクロスポリンなどが用いられているが、副作用などの面でより有用な乾癬治療剤が望まれている(皮膚疾患最新の治療 '９７－'９８、ｐ４－７、１０６－１０７)。

アラキドン酸代謝異常に起因する皮膚疾患の代表例として、他に下記の疾患が挙げられる。

肥満細胞症： 皮膚で増殖した肥満細胞からヒスタミンなどが放出され、皮膚の潮紅と蕁麻疹を呈する症状である。これらの症状は主としてヒスタミンによると考えられているため抗ヒスタミン薬が使用されるが、ＰＧ合成阻害剤を投与すると著明な改善が見られるヒスタミン抵抗性の症例(Main, R. A. et al. Br. J. Dermatol.107(Suppl. 22), 53 (1982))やＰＧＤ２の過剰産生が知られている(Roberts, L. J. et al. N. Engl. J. Med.303, 1400-1404 (1980))。

日光皮膚炎：中波長紫外線によりＰＧなどの炎症性メディエーターが血管拡張を惹起すると考えられている。

基底細胞癌あるいは有刺細胞癌（いずれも皮膚癌）：ＰＧが増加しており、その腫瘍の増殖にＰＧが関与する事が示唆されている(Vanderveen, E. E. et al. Arch.Dermatol. 122, 407-412(1986))。

一方、4-アミノ-2-エトキシメチル-α,α-ジメチル-１Ｈ－イミダゾ[4,５－ｃ]キノリン－１－エタノール（Ｒ８４８）は、 下記の薬理作用が知られている化合物である。

1)抗ウイルス作用：ヘルペスウィルス(Tomai. MA. et al. Antiviral Res. 28, 253-264(1995))感染系での抗ウィルス作用が報告されている。

2）サイトカイン誘導作用： ＩＦＮ、インターロイキン類(ＩＬ－１、ＩＬ－６、ＩＬ－８)や腫瘍壊死因子α(ＴＮＦ－α)の産生を誘導することが報告されている(Wagner et al. Cytokine 9 837-845 (1997))。

Ｒ８４８と 1-(2-メチルプロピル)－1H-イミダゾ[4,5-c]キノリン-4-アミン（イミキモド）について、Ｔｈ２型サイトカイン産生阻害作用を利用したアレルギー性

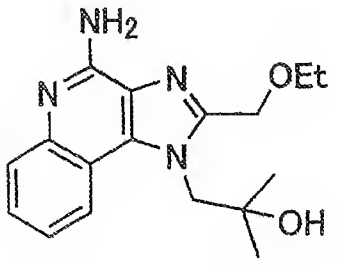
皮膚炎への医薬適用については公知である（WO 98/17279）。また、イミキモドについては、アラキドン酸代謝異常に起因する皮膚疾患への適用が本発明者らにより特許出願されている（特開 2000-247884）。しかし、Ｒ８４８がアラキドン酸代謝異常に起因する皮膚疾患に何らかの予防／治療効果を示すことに関して、上述の先行技術文献は何も記載していない。むしろ、イミキモドに無く、Ｒ８４８にのみ認められるＴＮＦ－αの産生誘導作用（Wagner et al. Cytokine 9 837-845 (1997)）は、ＴＮＦ－αの皮膚炎症惹起作用（Kondo, S et al. Eur. J. Immunol. 27, 1713-8(1997)）と相まって、Ｒ８４８の皮膚炎症惹起の可能性を示唆するものである。

発明の開示

本発明の課題は、アラキドン酸代謝亢進に起因する皮膚疾患、即ち、ＰＧ、ＬＴ等の産生亢進に起因する皮膚疾患を治療および／または予防するための新規な皮膚疾患治療剤の提供である。

本発明者らは、すでにイミキモドのアラキドン酸誘発マウス耳浮腫抑制作用を見いだし、乾癬などの皮膚疾患治療剤の発明として特許出願している（特開 2000-247884、前出）。しかし、今回、イミキモドの類縁化合物Ｒ８４８が極めて強く持続性のあるアラキドン酸誘発マウス耳浮腫抑制作用を示すことを発見し、本発明を完成した。すなわち本発明の要旨は、以下の［1］～［6］で表される。

［1］ 下式で表される化合物



（4-アミノ-2-エトキシメチル-α,α-ジメチル-１Ｈ－イミダゾ[4,5－c]キノリン－１－エタノール、以下、Ｒ８４８と略す）またはその酸付加塩または溶媒和物

を有効成分とするアラキドン酸代謝亢進に起因する皮膚疾患の予防および／または治療のための薬剤。

［2］ アラキドン酸代謝亢進に起因する皮膚疾患が乾癬、紫外線皮膚炎、肥満細胞症、基底細胞癌または有刺細胞癌である［1］記載の薬剤。

［3］ 経口投与用剤形である［1］または［2］に記載の薬剤。

［4］ 約０．１～約１０００ｍｇ／日の投与単位用量のＲ８４８を含有する［3］記載の薬剤。

［5］ 非経口投与用剤形である［1］または［2］に記載の薬剤。

［6］約０．１～約５０ｍｇ／日の投与単位用量のＲ８４８を含有する外用剤である［5］記載の薬剤。

本発明において、「アラキドン酸代謝昂進に起因する皮膚疾患」とは，アラキドン酸代謝経路（アラキドン酸カスケード）を構成するアラキドン酸およびその代謝物の異常な増加によって生じる皮膚疾患を意味し、具体的疾患名としては、乾癬、紫外線皮膚炎、肥満細胞症、基底細胞癌または有刺細胞癌が挙げられる。アラキドン酸代謝物とは、（1）シクロオキシゲナーゼ酵素により産生されるプロスタグランジン類：ＰＧＥ（プロスタグランジンＥ）、ＰＧＦ、ＰＧＩ、ＴＸＡ（トロンボキサンＡ）など、（2）リポキシゲナーゼ酵素により産生されるロイコトリエン類： ＬＴＢ４、ＬＴＣ、ＬＴＤ、ＬＴＥ等、および（3）１２－ＨＥＴＥ等を意味し、これらのメディエーターが異常に増加した結果生じる炎症性の皮膚疾患が、本発明の適用対象である。

ただし、本発明における皮膚疾患には、ウィルスや細菌感染症、火傷凍傷、外傷による皮膚炎症、膠原病（全身性エリテマトーデス、強皮症などの自己免疫疾患）に伴う皮膚疾患、異種免疫反応によって生じるアレルギー性皮膚疾患（蕁麻疹、接触皮膚炎、アトピー性皮膚炎など）は含まれない。

以下に本発明の有効成分とその製造方法について述べる。

本発明の有効成分であるＲ８４８およびその酸付加塩は、公知の方法に準じて容易に合成することができる。例えば、WO98/17279 に記載の方法に準じればよい。Ｒ８４８の酸付加塩の酸としては、薬理学的に許容される酸であれば特に限定されず、水和物等の溶媒和物であってもよい。酸付加塩は、無機酸（例えば、塩酸、臭化水素酸、硫酸、リン酸および硝酸等）や酢酸、蓚酸、酒石酸、コハク酸、リンゴ酸、アスコルビン酸、安息香酸、タンニン酸、パモイン酸、アルギニン酸、ポリグルタミン酸、ナフタレンスルホン酸、ナフタレンジスルホン酸およびポリガラクトゥロン酸(polygalacturonic acid)のような有機酸とで形成される。塩酸、硫酸、酢酸、蓚酸、アスコルビン酸などが好適な酸付加塩である。

Ｒ８４８およびその塩は、種々の製剤形態（例えば、液剤、固形剤、カプセル剤等）をとりうる。経口投与のための剤型としては、例えば、錠剤、カプセル剤、丸剤、顆粒剤、散剤、液剤、懸濁剤などが挙げられ、非経口投与のための剤型としては、例えば、注射用水性剤、もしくは油性剤、軟膏剤、クリーム剤、ローション剤、エアロゾル剤、坐剤、貼付剤などが挙げられる。

また、所望の作用を損なわない他の活性材料、または抗生物質、抗真菌剤、他の抗炎症剤または抗ウイルス性化合物のような所望の作用を補足する材料と混合して用いることもできる。

経口治療投与の目的のために、活性成分は賦形剤に組み込み、液剤、粉剤、散剤、錠剤、トローチまたはカプセルで用いることができる。薬学的に相溶性のある結合剤および／またはアジュバント材料を組成物の一部として含むことができる。錠剤、丸剤、カプセルおよびトローチ等は、任意の、以下の性質が類似している成分または化合物を含むことができる：微結晶性セルロース、ガムトラガカントまたはゼラチンのような結合剤；澱粉またはラクトースのような賦形剤；アルギン酸、リモゲル（rimogel）またはコーンスターチのような分散剤；ステアリン酸マグネシムまた

はステローツ（Sterotes）のような潤滑剤；コロイド状二酸化ケイ素のような滑剤；スクロースまたはサッカリンのような甘味料；または、ペッパーミント、サリチル酸メチルまたはオレンジ風味剤のような風味剤。投与単位形態がカプセルの場合、前述の種類の材料に加えて、脂肪油のような液体キャリヤーを含むことができる。さらに、投与単位形態は、投与単位の物理的形態を改良する種々の他の材料、例えば糖の被膜、シェラックまたは溶腸性剤を含むことができる。Ｒ８４８および薬学的に許容できる塩は、エリキシル、懸濁液、シロップ、ウエハース、またはチューインガム等の成分として投与することができる。シロップは、活性成分に加えて、甘味料としてのスクロース、および特定の防腐剤、染料および着色剤ならびに風味料を含み得る。

また、Ｒ８４８は、移植およびマイクロカプセル投与系を含む徐放性製剤として調製されうる。担体としては、エチレン酢酸ビニル、ポリ無水物、ポリグリコール酸、コラーゲン、シリコン、ポリオルトエステルおよびポリ乳酸のような生分解性で生物適合性のポリマーを用いることができる。そのような製剤を調製する方法は当業者に明らかであり、材料も市販品として入手できる。　また、リポソーム懸濁液も適当な脂質（例えばステアロイルホスファチジルエタノールアミン、ステアロイルホスファチジルコリン、アラカドイルホスファチジルコリンおよびコレステロール）を担体に用いて当業者に知られている方法によって調製することができる。

Ｒ８４８を有効成分として含有する非経口、皮内、皮下または局所適用のために用いられる溶液または懸濁液は以下の成分を含むことができる。注入用水、塩水溶液、固定油(fixedoil)、　ポリエチレングリコール、グリセリン、プロピレングリコールまたは他の合成溶媒のような滅菌希釈剤；ベンジルアルコールまたはメチルパラベンのような殺菌剤；アスコルビン酸または亜硫酸水素ナトリウムのような酸化防止剤；エチレンジアミン四酢酸のようなキレート化剤；アセテート、クエン酸

またはリン酸のような緩衝剤および塩化ナトリウムまたはデキストロースのような張度を調整するための薬剤など。非経口製剤は、アンプル、使い捨て注射器またはガラスまたはプラスチック製の複投与量バイアル中に封入し得る。注射剤は、常法により調製することができ、例えば、当該化合物を適切な溶剤（例えば、滅菌された水、緩衝液、生理食塩水等）に溶解した後、フィルター等で濾過して滅菌し、次いで無菌的な容器に充填することにより調製することができる。静脈内に投与する場合、好ましいキャリヤーは生理食塩水またはリン酸緩衝食塩水(PBS)である。

本発明において、外用剤は特に好適な剤型の一つである。Ｒ８４８は、近似の化学構造を有するイミキモド、1-(2-メチルプロピル)－1H-イミダゾ[4,5-c]キノリン-4-アミンと比較した場合、少なくとも２０倍水溶性が高いという特性を持つ（ｐＨ 2.5、5.5,および７での水溶解度 1000μg/ml 以上）。この特性により、本発明の医薬は製剤化が容易なだけでなく、中枢や他の組織への有効成分移行性が低い。また、患部での効果は持続的である。このように本発明のＲ８４８含有製剤は、外用剤として特に優れた性質を有する。

外用剤の剤型は、特に限定されるものではなく、クリーム状、ペースト状、ジェリー状、ゲル状、乳液状、液状等の形状になされたもの（軟膏剤、リニメント剤、ローション剤等）が薬物及び経皮吸収促進剤を溶解または混合分散させたものを支持体上に展延したもの（パップ剤等）、粘着剤中に上記薬物及び経皮吸収促進剤（本発明３の場合使用）を溶解または混合分散させたものを支持体上に展延したもの（プラスター剤、テープ剤等）などが挙げられる。上記基剤としては、薬学的に許容しうるものであればよく、軟膏剤、リニメント剤、ローション等の基剤として従来公知のものを用いることができ、例えば、アルギン酸ナトリウム、ゼラチン、コーンスターチ、トラガントガム、メチルセルロース、ヒドロキシエチルセルロース、カルボキシメチルセルロース、キサンタンガム、デキストリン、カルボキシメチル

デンプン、ポリビニルアルコール、ポリアクリル酸ナトリウム、メトキシエチレン－無水マレイン酸共重合体、ポリビニルエーテル、ポリビニルピロリドン等のポリマー；ミツロウ、オリーブ油、カカオ油、ゴマ油、ダイズ油、ツバキ油、ラッカセイ油、牛油、豚油、ラノリン等の油脂類；白色ワセリン、黄色ワセリン；パラフィン；ハイドロカーボンゲル軟膏（例えば、商品名プラスチベース、大正製薬社製）；ステアリン酸等の高級脂肪酸；セチルアルコール、ステアリルアルコール等の高級アルコール；ポリエチレングリコール；水などが挙げられる。さらに必要に応じて、カオリン、ベントナイト、酸化亜鉛、酸化チタン等の無機充填剤；粘度調節剤；老化防止剤；ｐＨ調節剤；グリセリン、プロピレングリコール等の保湿剤などを添加してもよい。

外用基剤（軟膏、クリームなど）の場合、一般に膏体１ｇあたり、１～１０００ｍｇの、好ましくは 3~3００㎎のＲ８４８あるいはその塩を有効成分として含有させることができる。

本発明の医薬は、投与形態や投与量には特に限定は無く、適宜当業者が用いうる方法で有れば良いが、下記の方法が例示される。

すなわち、経口投与の場合、吸入剤またはカプセル剤、錠剤、顆粒剤などの剤形で投与することができ、一般に、経口投与の場合、大人では１日当たり約１～約１０００ｍｇの範囲、好ましくは約１０～約５００ｍｇの範囲を 1 回または数回に分けて投与する。

非経口投与の場合、水溶性懸濁液による皮下あるいは静脈注射剤、点滴剤、あるいは軟膏などの剤形で用いることができる。注射剤の場合、投与量は、患者の症状、年齢、体重等により異なり、また、対象疾患を有効に治療するに充分な量を適宜使用することになるが、約０．１～約５００ｍｇの範囲、好ましくは約３～約１００ｍｇの範囲を１回または数回に分けて投与することができる。外用経皮製剤（液剤、油性軟膏、親水性軟膏あるいはクリーム）の場合、使用量は、疾患の種類や症状の

程度、患部の大きさ等によって異なるが、外用剤の量として、１日当たり０．１～１００ｇ、さらに好ましくは、１～１０ｇを１回又は適当な回数に分けて患部に適用すればよい。

産業上の利用可能性

本発明により、アラキドン酸代謝異常に起因する各種皮膚疾患（乾癬、紫外線皮膚炎、肥満細胞症、基底細胞腫、有刺細胞癌等）が安全かつ効果的に治療できる。

実施例

以下、実施例を挙げて本発明を更に詳細に説明するが、本発明はこれらの実施例になんら限定されるものではない。

製剤例１　注射用液剤

精製水（２mL）に、Ｒ８４８（２００mg）およびエリスリトール（２５０mg）を溶解し、非経口投与用液剤を調製する。

製剤例２　経口用液剤

精製水（１mL）に、Ｒ８４８（２００mg）、グリセリン（２００mg）、クエン酸（６mg）およびクエン酸ナトリウム（２０mg）を溶解し、経口投与用液剤を調製する。

製剤例３　クリーム

Ｒ８４８（２ｇ）にクロタミトン５ｇ、ニッコール（ＴＳ－１０）５ｇ、流動パラフィン３ｇ、ミリスチン酸イソプロピル１５ｇを加え、７０℃に加温して溶解する。これにカルボキシビニルポリマー１ｇを水６０ｇに膨潤した溶液を加え、撹拌して乳化する。次に、ジイソプロパノールアミン０．５ｇを水９．７５ｇに溶か

した溶液を加え、均一になるまで撹拌してＲ８４８を有効成分として含有するクリームを得る。

製剤例４　油性軟膏

Ｒ８４８（１０ｇ）を精製水（３０ｇ）に溶解させ、ヘキシレングリコール（１２０ｇ）と混合する。これを溶融させた白色ワセリン（７００ｇ）、白色ワックス（８０ｇ）とプロピレングリコールステアレート（２０ｇ）の混合物に添加し、温度を下げながら均質に撹拌してＲ８４８を有効成分として含有する軟膏を得る。

実施例１

アラキドン酸誘発皮内反応に対するＲ８４８の抑制作用

１）ＢＡＬＢ／ｃマウス(雌、6週令)を日本チャールズリバー(神奈川、日本)より購入し、８週令まで予備飼育し使用した。

２)試験薬物：Ｒ８４８（フリー体)

３)Ｒ８４８を秤量後、アセトンに２０ｍｇ／ｍｌと２ｍｇ／ｍｌの濃度に懸濁した。ジエチルエーテル麻酔下でマウス左耳介の表裏に１０μｌずつＲ８４８懸濁液を塗布した(Ｒ８４８投与群)。コントロール群としてアセトンだけを左耳介の表裏に１０μｌずつ塗布したマウスを用意した。

４)アラキドン酸塗布：Ｒ８４８あるいはアセトン塗布４時間後に１０％アラキドン酸(CAYMAN CHEMICAL. Co.、ミシガン、アメリカ)をＲ８４８投与群とコントロール群の左耳介の表裏に１０μｌずつ塗布した。

５)皮内反応の測定：Ｒ８４８あるいはアセトン塗布前(抗原惹起せず)と１０％アラキドン酸塗布１時間後(抗原惹起したもの)にジエチルエーテル麻酔下でDial Thickness Gage(Mitutoyo Co.、東京、日本)で左右両耳介の厚さを測定した。皮内反応は、(抗原惹起した左耳介の厚さ)－(抗原惹起しない右耳介の厚さ)で表現した。

6)解析：スチューデントｔ－テスト(Student's t-test)検定で有意差検定を行った。１％以下の危険率で有意差が認められた場合は、ｐ＜０．０１の表示で表した。その結果を表１に示す。

表1．Ｒ８４８のアラキドン酸誘発皮内反応に対する抑制効果

	N	皮内反応（平均値：μm）	ＳＥＭ	有意差検定
対照群	5	２０８．０	１４．６	
R848 (2 mg/ml)	5	６０．０	２３．０	p<0.01
R848 (20mg/ml)	5	６２．０	１３．２	p<0.01

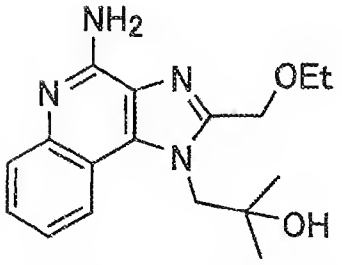
表１から明らかなように、Ｒ８４８（2mg/ml、20mg/ml）は塗布後４時間後においても有意なアラキドン酸誘発皮内反応抑制効果を示した。この結果は、Ｒ８４８含有製剤がアラキドン酸代謝亢進に起因する皮膚疾患の治療剤または予防剤として有効である事を示す。

表２．酸性～中性領域でのＲ８４８およびイミキモドの水溶解度

1ｍｌあたりの最大溶解量（μｇ）			
	ｐＨ ２．５	ｐＨ ５．５	ｐＨ ７．４
イミキモド	３２．４	５０．４	３．４
Ｒ８４８	＞１０００	１０００＞	１０００＞

請求の範囲

1. 下式で表される化合物



（Ｒ８４８：4-アミノ-2-エトキシメチル-α,α-ジメチル-１Ｈ－イミダゾ[4,5－c]キノリン－１－エタノール）またはその酸付加塩または溶媒和物を有効成分として含有するアラキドン酸代謝亢進に起因する皮膚疾患の予防および／または治療のための薬剤。

2. アラキドン酸代謝亢進に起因する皮膚疾患が乾癬、紫外線皮膚炎、肥満細胞症、基底細胞癌または有刺細胞癌である、１に記載の薬剤。

3. 経口投与用剤形である１または２に記載の薬剤。

4. 約１～約１０００ｍｇ／日の投与単位用量のＲ８４８を含有する、３に記載の薬剤。

5. 非経口投与用剤形である１または２に記載の薬剤。

6. 約０．１～約５００ｍｇ／日の投与単位用量のＲ８４８を含有する外用剤である５に記載の薬剤。

INTERNATIONAL SEARCH REPORT

International application No.
PCT/JP01/09575

A. CLASSIFICATION OF SUBJECT MATTER
Int.Cl[7] C07D471/04, A61K31/4745, A61P17/00, 17/02, 17/06, 35/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
Int.Cl[7] C07D471/04, A61K31/4745

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
CAPLUS (STN), REGISTRY (STN)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5389640 A (Minnesota Mining and Manufacturing Company), 14 February, 1995 (14.02.1995), especially, Column 11, lines 58 to 68; Column 35, "EXAMPLE 99" & WO 92/15582 A1 & JP 6-504789 A & AU 2715795 A & HU 67026 A & CA 2104782 A & IE 920605 A & ZA 9201540 A & NO 933069 A & EP 582581 A & NZ 241784 A & CZ 9301788 A & EP 872478 A2	1-6
Y	WO 98/24436 A2 (Minnesota Mining and Manufacturing Company), 11 June, 1998 (11.06.1998), especially, page 1, line 23 to page 2, line 20; page 18, Claim 15 & AU 5368698 A & NO 992638 A & US 5939090 A & CZ 9901955 A & EP 942724 A & BR 9713677 A	1-6

☒ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
15 January, 2002 (15.01.02)	29 January, 2002 (29.01.02)
Name and mailing address of the ISA/ Japanese Patent Office Facsimile No.	Authorized officer Telephone No.

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/JP01/09575

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 00/40228 A2 (3M INNOVATIVE PROPERTIES COMPANY), 13 July, 2000 (13.07.2000) & AU 2721600 A	1-6
A	WO 98/17279 A1 (Minnesota Mining and Manufacturing Company), 30 April, 1998 (30.04.1998) & AU 5164198 A & NO 991908 A & EP 938315 A & US 6039969 A & HU 9904665 A	1-6

allowed, and as the substrate agents for the soft ointment agents, riniment, lotion etc., it is possible to use the materials that are well-known from the previous technology, for example, sodium arginate, gelatin, corn starch, toragant gum, methyl cellulose, hycroxy ethyl cellulose, carboxy methyl cellulose, xatance gum, dextrin, carboxy methyl starch, polyvinyl alcohol, sodium polyacrylate, methoxy ethylene – maleic acid anhydride copolymer material, polyvinyl ether, polyvinyl pyrolidone, etc., polymers; natural wax, olive oil, cocoa oil, sesame oil, soybean oil, camellia oil, peanut oil, beef tallow, lard, lanoline etc., fatty type matter; white color Vaseline, yellow color Vaseline; paraffin; hydrocarbon gel soft ointment (for example, product with the trade name of Plastibase, manufactured by Shosei Pharmaceutical Company); stearic acid etc., high homologous order aliphatic acids; cetyl alcohol, stearyl alcohol, etc., high homologous order alcohols; polyethylene glycol; water etc. Then, depending on the requirements, it is also a good option if kaolin, bentonite, zinc oxide, titanium oxide etc., inorganic filler agents; viscosity regulating agents, anti-ageing agents, pH regulating agents, glycerine, propylene glycol etc., moisture preserving agents, etc., are added.

In the case of the external use substrate agent (soft ointment, cream etc.), usually, relative to 1 gram of the ointment material, in the range of 1 ~ 1000 mg, and preferably, in the range of 3 ~ 300 mg of R848 or its salts, are contained as the active ingredients.

Regarding the drug according to the present invention, there are no particular limitations relative to the administration state or the administered amount, and it is a good option as long as it is used according to the methods applied by the persons skilled in the industry, however, the described here below methods can be shown as examples.

Namely, in the case of oral administration, it is possible to be administered as an inhalation agent or a capsule agent, a pill agent, a powder agent etc., agent form, and usually, in the case of oral administration, it is administered for adults daily in the range of approximately 1 ~ approximately 1000 mg, and preferably in the range of approximately 10 ~ approximately 500 mg, at one time or divided in several times.

In the case of non-oral administration, it is possible to use as an aqueous suspension under the skin or as a venous injection agent, a dripping agent, or a soft ointment etc., agent forms. In the case of injection agent, the dosage amount varies depending on the patient symptoms, age, body weight, etc., and also, even though an appropriate amount is applied so that it is sufficient for the effective treatment of the symptoms of the patient, it can be administered in an amount in the range of approximately 0.1 ~ approximately 500 mg, and preferably, in an amount that is in the range of approximately 3 ~ approximately 100 mg, at one time, or divided into several times. In the case of external use skin application manufactured agent (liquid agent, oily soft ointment, hydrophilic soft ointment or cream), the used amount varies depending on the type of the disease and the degree of the symptoms, the size of the affected part, etc., however, as the amount of the external use agent, daily, it is a good option if it is appropriately used on the diseased part in an amount that is in the range of 0.1 ~ 100 g, and then more preferably, in the range of 1 ~ 10 grams, at one time, or separated in several times.

Technological Sphere of Advantageous Application

According to the present invention, it is possible to safely and also effectively treat different types of skin diseases caused by the abnormal arachidonic metabolism (psoriasis, ultraviolet dermatitis, mastocytoma, basiloma, squamous cell carcinoma, etc.).

Practical Examples

Here below, practical application examples are presented and the present invention is described in further details, however, the present invention is by no means limited by these practical application examples.

Manufactured Agent Example 1

Solution agent used for injections

In purified water (2 ml), R848 (200 mg) and erithritol (250 mg) are dissolved, and by that a non-oral administration solution agent is manufactured.

Manufactured Agent Example 2

Solution agent used for oral administration

In purified water (1 ml), R848 (200 mg) and glycerine (200 mg), citric acid (6 mg) and sodium citrate (20 mg) are dissolved and by that an oral administration type liquid agent is manufactured.

Manufactured Agent Example 3

Cream

In the R848 (2 g), 5 grams of crotamiton, 5 grams of niccol (TS-10), 3 grams of liquid paraffin, and 15 grams of isopropyl myristate, are added, and this is heated to a temperature of 70oC, and dissolved. To that material, a solution obtained as 1 gram of carboxy vinyl polymer has been allowed to swell in 60 grams of water, is added, and it is emulsified while stirring. After that, a solution obtained as 0.5 grams of diisopropanol amine was dissolved in 9.75 grams of water, was added and it was stirred until the material became homogeneous, and a cream, containing R848 as its active ingredient, was obtained.

Manufactured Agent Example 4

Oily soft ointment

R848 (10 grams) were dissolved into purified water (30 grams), and this was mixed with hexylene glycol (120 grams). This was added to a mixture of molten, white color

glycerine (700 grams), white color wax (80 grams), and propylene glycol stearate (20 grams), and as the temperature was decreased it was stirred into a homogeneous material, by that a soft ointment containing R848 as its active ingredient, was obtained.

Practical Implementation Example 1

R848 suppressing action relative to arachidonic acid provoked reaction inside the skin

1) BALB/c mouse (female, 6 weeks old) was purchased from Nippon Charles River (Shinakawa, Japan), and it was prepared and raised until it was 8 weeks old, and it was then used.
2) Experimental medicine: R848 (cream material)
3) The R848 was weighted and after that it was suspended in acetone so that the concentrations became concentrations of 20 mg/ml and 2 mg/ml. Under diethyl ether anesthesia, on the front and the back of the left ear of the mouse, 10 microliters each of the R848 suspension was coated (R848 administration group). As the control group, mouse was used where only acetone was used and that was applied on the front and the back of the left ear at an amount of 10 microliters each.
4) Arachidonic acid application: 4 hours after the application of the R848 or the acetone, 10 % arachidonic acid (CAYMAN CHEMICAL CO., Michigan, USA), was applied on the front and back of the left ear of the R848 administered group and the control group, at 10 microliters each.
5) Measurement of the reaction inside the skin: Prior to the application of the R848 or the acetone (without provoking an antigen) and one after the application of the 10 % arachidonic acid (after the provocation of the antigen) under diethyl ether anesthesia, the thickness of both the right and the left ears was measured by using a Dial Thickness Gage (manufactured by Mitutoyo Co., Tokyo, Japan). The reaction inside the skin was expressed as the (thickness of the antigen provoked left ear) – (thickness of the non-antigen provoked right ear).
6) Analysis: According to the Student's t-test inspection, the inspection for intentional differences was conducted. In the case when the intentional difference was observed at no more than 1 % or less risk ratio, it was represented by an indication of $p<0.01$. The results from this analysis are presented in Table 1.

Table 1. Suppression effect of R848 on the arachidonic acid induced reaction inside the skin

	N	Reaction inside the skin (average value: microns)	SEM	Intentional difference inspection
Comparison Group	5	208.0	14.6	
R848 (2 mg/ml)	5	60.0	23.0	P<0.01
R848 (20 mg/ml)	5	62.0	13.2	P<0.01

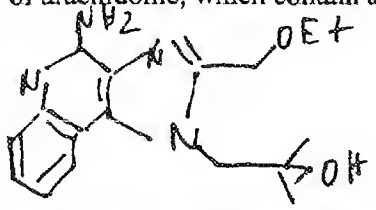
As it is clear from the table here above, in the case of the R848 (2 mg/ml, 20 mg/ml), even after 4 hours after the application, an intentional suppression effect on the arachidonic acid induced reaction inside the skin, was observed. This results shows that the R848 containing manufactured agent is effective as a treating agent or as a prevention agent relative to skin diseases induced by the accelerated metabolism of arachidonic acid.

Table 2. Water solubility of R848 and imichimodo in acidic ~ neutral ranges

Maximum dissolved amount (micrograms) in 1 ml			
	pH 2.5	pH 5.5	pH 7.4
Imichimodo	32.4	50.4	3.4
R848	>1000	1000>	1000>

Range of the Claims

1. Drug for preventing and/or treating skin diseases induced by the accelerated metabolism of arachidonic, which contain a compound with the described here below formula



(R848: 4- amino-2-ethoxymethyl-α,α-dimethyl-1H-imidazo [4, 5c]quinoline-1-ethanol, here below called R848) or its acid adduct salts or solvates, as their active ingredient.

2. Drug according to the above described [1], where the skin disease induced by the accelerated metabolism of the arachidonic acid are psoriasis, ultraviolet dermatitis, mastocytoma, basiloma or squamous cell carcinoma.

3. Drug according to the above described [1] or [2] where it is a drug form, which is orally received.

4. Drug according to the above described [3] where it contains approximately 0.1 ~ approximately 1000 mg/day imparted units amount of R848.

5. Drug according to the above described [1] or [2] where it is a drug form, which is not orally received.

6. Drug according to the above described [5] where it is an external use drug, which contains approximately 0.1 ~ approximately 50 mg/day imparted units amount of R848.

Translated by Albena Blagev ((651) 704-7946 (w), (651) 735-1461 (h))

08/19/02

[Note: Names, addresses, company names and brand names are translated in the most common manner. Japanese language does not have singular or plural words unless otherwise specified by a numeral prefix or a general form of plurality suffix.]

Description of the Invention

(54) Title: Remedies for Arachironic Acid-Induced Skin Diseases

(57) Abstract:

Drugs for preventing and/or treating arachidonic acid-induced skin diseases, which contain 4-amino-2-ethoxymethyl-α,α dimethyl-1H-imidazo [4, 5-c]quinoline-1-ethanol: R848, or its acid adduct salts or solvates, as their active ingredient. By using these drugs, various skin diseases caused by the accelerated arachidonic metabolism (psoriasis, ultraviolet dermatitis, mastocytoma, basiloma, squamous cell carcinoma, etc.) can be safely and effectively treated.

Description of the Invention

Remedies for Arachironic Acid-Induced Skin Diseases

Technological Field

The present invention is an invention about a skin disease treatment remedies. And then in more details, the present invention is an invention about drugs for preventing and/or treating arachidonic acid-induced skin diseases caused by the accelerated arachidonic metabolism, like psoriasis, ultraviolet dermatitis, mastocytoma, basiloma, squamous cell carcinoma, etc.

Technological Background

The generated through the arachidonic acid induced metabolism conditions prostaglandine (PG) and leucotolyene (LT) are related to physiological function regulation like stomach acid component secretion or blood plate cohesion, different types of smooth muscle contraction etc., and together with that they are fatty acid system information transmission materials (mediators). The PG and the LT are important for the maintenance of the constancy of the living body, and it is considered that in the case of some skin diseases, their excessive generation is the main cause of the disease.

As representative examples of such skin diseases, first, there is the psoriasis disease. The psoriasis is a chronic disease which indicates abnormal benign increase of the front skin cells, and the invasion of multiformity of core white blood cells inside the surface skin, and because of the described here below reasons (1) ~ (4), it is considered that it is a disease related strongly to abnormal products generated by the arachidonic acid

metabolism. (1) In the psoriasis disease skin part, the PG, arachidonic acid and 12-HETE, are increased (Hammerson, S. et al. Proc. Nat. Acad. Sci. USA. 72, 5130-5134 (1975)), (2) if LTB4 is patched onto the human skin, small abscesses inside the surface skin, which look like the psoriasis skin disease parts, are formed (Camp, S. et al. J. Invest. Dermatol. 82, 202 – 204 (1984), (3) through the blood vessel expansion effect of the PG and through the blood vessel permeability acceleration due to the Leucotolyene C, D and E (LTC, LTD, LTE), a skin reddening and swelling reaction, are provoked, (4) through Leucotolyene 5, 12-dihydroxy material (LTB4), the excessive idleness of a large number of white blood cells is increased, and there is a formation of abscesses under and inside an angle layer that is characteristic of psoriasis etc. At the present time, Torechinate (Vitamin A derivative material), active form Vitamin D3, Cyclosporin etc., are used, however, effective psoriasis disease remedies that have a secondary effect etc., at the surface, are desirable (The newest skin disease remedies '97 ~ '98, p 4 – 7, 106-107).

As representative examples of skin diseases caused by abnormal arachidonic acid metabolism, there are the described here below diseases.

Mastocytoma: It is a condition where histamine etc., is released from the increased in the skin mastocystoma, and skin flushing and pale measles are presented. It is considered that these symptoms are mainly caused by the histamine, and because of that antihystamine drugs are used. However, if an agent hindering the PG synthesis is imparted, cases of histamine resistance where a significant improvement can be seen are known (Main, R. A. et al. Br. J. Dermatol. 107 (Suppl. 22) 53 (1982)) and PGD2 excessive generation, are known (Roberts, L. J. et al. N. Engl. J. Med. 303, 1400 – 1404 (1980)).

Sunlight dermatitis: It is considered that the caused by the medium wavelength ultraviolet rays PG etc., inflammation mediators provoke the expansion of the blood vessels.

Basiloma and squamous cell carcinoma (both skin cancers): It is suggested that the PG is increased and the PG participates in the increase of these tumors (Vanderveen, E. E. et al. Arch. Dermatol. 122, 407-412 (1986)).

On the other hand, the 4-amino-2-ethoxymethyl -α, α - dimethyl – 1H – imidazo [4, 5-c] quinoline – 1- ethanol (R848), is a compound that is known to have the described here below pharmacological effects.

1) The antiviral effect: The antiviral effect in a herpes virus infected system has been reported (Tomai, MA. Et al. Antiviral Res. 28, 253-264 (1995)).
2) Citokine inducement effect: The fact that the generation of IFN, intaloikin type (IL-1, IL-6, IL-8) or tumor destruction death causing element α (TNF-α) causes the inducement, has been reported (Wagner et al. Cytokine 9 837-845 (1997)).

Regarding R848 and 1-(2-methylpropyl) –1H-imidazo[4, 5-c]quinoline-4-amine (imichimodo), the appropriate use of treatment of allergic skin inflammation by the advantageous use of the Th2 type cytokine generation hindrance effect, is well known (WO 98/17279). Also, regarding the imichimodo, a patent application has been filed by

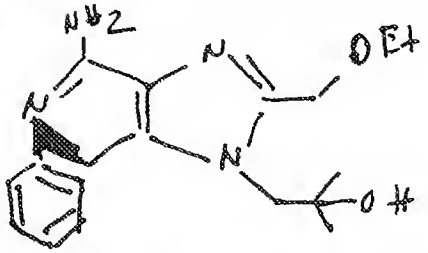
the authors of the present invention regarding its appropriate use for skin diseases that are caused by abnormal arachidonic acid metabolism (Japanese Patent Application Number Hei-Sei 2000-247884). However, in the previously described preceding technical references there has been no reporting whatsoever relative to an indication that the R848 has any prevention and/or treatment effect on skin diseases induced by abnormal arachidonic acid metabolism. Rather, except for the imichimodo, the TNF-α production inducing effect that has been recognized only in the R848 (Wagner et al. Cytokine 9 837-845 (1997)) has been combined with the TNF-α skin inflammation provocation effect (Kondo, S et al. Eur. J. Immunol. 27, 1713-8 (1997)), and it indicates the possibility of the R848 skin inflammation provocation.

Invention Description

The problem of the present invention is to suggest a novel skin disease treatment agent (remedy) for the treatment and/or the prevention of skin diseases caused by accelerated arachidonic acid metabolism, namely, skin diseases caused by the accelerated production of PG, LT etc.

The authors of the present invention have already observed the suppression effect of the imnichimodo on the swelling of the mouse ear induced by arachidonic acid, and a patent application for an invention for skin disease remedy for psoriasis, etc. has been filed (Japanese Patent Application 2000-247884, previously issued). However, at this time, it has been discovered that the imichimodo type afforestation compound R848 is a material that shows an effect of suppressing the swelling of mouse ear induced by arachidonic acid, which has extremely strong persistence, and by that the present invention has been accomplished. Namely, the essential elements of the present invention are shown in the described here below [1] ~ [6].

[1] Drugs for preventing and/or treating skin diseases induced by the accelerated metabolism of arachidonic, which contain a compound with the described here below formula



(4- amino-2-ethoxymethyl-α,α-dimethyl-1H-imidazo [4, 5c]quinoline-1-ethanol, here below called R848) or its acid adduct salts or solvates, as their active ingredient.

[2] Drug according to the above described [1], where the skin disease induced by the accelerated metabolism of the arachidonic acid are psoriasis, ultraviolet dermatitis, mastocytoma, basiloma or squamous cell carcinoma.

[3] Drug according to the above described [1] or [2] where it is a drug form, which is orally received.

[4] Drug according to the above described [3] where it contains approximately 0.1 ~ approximately 1000 mg/day imparted units amount of R848.

[5] Drug according to the above described [1] or [2] where it is a drug form, which is not orally received.

[6] Drug according to the above described [5] where it is an external use drug, which contains approximately 0.1 ~ approximately 50 mg/day imparted units amount of R848.

According to the present invention, the term "skin diseases induced by the accelerated metabolism of arachidonic acid" has the meaning of skin diseases generated by the abnormal increase of the arachidonic acid, which forms the structure of the arachidonic acid metabolism circumstances (arachidonic acid cascade) and its metabolism materials, and in more details, they are psoriasis, ultraviolet dermatitis, mastocytoma, basiloma, squamous cell carcinoma, etc. Regarding the arachidonic acid metabolism materials, this means (1) the generated by cyclooxygenaze enzyme prostaglandine type: PGE (prostaglandine E), PGF, PGI, TXA (tromboxane A), etc., (2) the produced by the lipoxygenaze enzyme leucotolyene type: LTB4, LTC, LTD, LTE etc., and (3) 12-HETE, etc., and the inflammation skin diseases that are caused as a result from the abnormal increase of these mediators, are the subject of use of the present invention.

However, in the skin diseases according to the present invention, the virus or bacteria infection diseases, burn and freeze wounds, skin inflammation symptoms caused by external wounds, skin diseases accompanying glue originating diseases (full body eritematodes, strong skin diseases, etc., autoimmune diseases), allergic skin diseases generated through unusual immune reaction (hives, contact skin inflammation, atopi skin inflammation etc.) are not included.

Here below the active ingredients according to the present invention and their manufacturing method, will be described.

The R848 and its acid adduct salts, which constitute the active ingredients of the present invention are materials that can be easily synthesized according to well known methods. For example, it is a good option if the method references according to the reported in the WO 98/17279, is used. As the acids of the acid adduct salts of R848, there are no particular limitations as long as they are acids that are pharmaceutically allowed, and it is also a good option if they are solvates of water etc. Regarding the acid adduct salts, they are formed by using inorganic acids (for example, hydrochloric acid, bromic acid, sulfuric acid, phosphoric acid and nitric acid, etc.), or acetic acid, oxalic acid, tartaric acid, succinic acid, malic acid, ascorbic acid, benzoic acid, tannic acid, pamoic acid, arginic acid, polyglutamic acid, naphthalenesulfonic acid, naphthalene disulphonic acid, and polygalacturonic acid, etc., organic acids. The slats from the hydrochloric acid,

sulfuric acid, acetic acid, oxalic acid, ascorbic acid etc., are the preferred acid adduct salts.

The R848 and its salts are obtained and sold in different manufactured agent conditions (for example, liquid agent, sold phase agent, capsule agent etc.). As an agent form in order to be used for oral administration, for example, there are the pill agent, capsule agent, spherical agent, particular agent, dispersed agent, liquid agent, suspended agent, etc., forms. And as agent forms for non-oral type administration, for example, there are the aqueous agent or oil type agent used for injections, the soft ointment agent, the cream agent, the lotion agent, the aerosol agent, the suppository, the adhered (patch) agent, etc.

Also, it is possible to admix and use other active ingredients as long as they do not deteriorate the desired effect, or it is possible to admix and use antibiotic materials, antibacterial agents, other anti-inflammation agents or antiviral compounds, etc., that promote the desired effect.

With the goal of oral medical treatment administration, it is possible that the active ingredient is incorporated and combined into an allotment agent, and it is used as a liquid agent, powder agent, dispersed agent, pill agent, torochi agent or capsule agent. It is also possible that a binding agent and/or an adjuvent agent, which are pharmaceutically compatible are contained as one part of the composition material. Regarding the pill agent, the spherical agent, the capsule or the torochi etc., it is also possible that they include a component or compound that is similar to the listed below materials: microcrystalline cellulose, gamutoragacanto or gelatine, etc., binding agents; starch powder or lactose, etc., allotment type agents; arginic acid, rimogel or corn starch etc., dispersing agents; magnesium stearate or Sterotes etc., lubricating agents; colloidal type silicon dioxide etc., slip agents, sucrose or saccharine etc., sweetening ingredients; or peppermint, methyl salicilate or orange flavoring agent, etc., flavoring agents. In the case when the administered unit state is a capsule state, in addition to the above-described types of materials, it is also possible to include an aliphatic oil type liquid material carrier. Then, regarding the administered unit state, in order to improve the physical condition of the administered unit, it is possible to include different types of other materials, for example, a sugar cover layer, shellac or a agents soluble in the digestive tract. The R848 and the pharmacologically allowed salts can be administered as components of elixirs, suspensions, syrups, or chewing gum etc. Regarding the syrups, in addition to the active ingredient as a sweetening agents, they include sucrose, and specific preservatives, dyeing materials, and coloring agents and together with that flavoring agents.

Also, the R848 is manufactured and sold as a slow release manufactured agent including a skin grafting and microcapsule administration system. As the carrier materials, it is possible to use vinyl ethylene acetate, polyanhydrides, polyglycolic acids, collagen, silicone, polyorthoesters and polylactic acid etc., biodegradable polymers that are useful for the living matter. Regarding the manufacturing method for the preparation of such manufactured agents, it is clear to people skilled in the industry, and the materials also can be procured as commercially available products. Also, it is possible to be

manufactured according to the method that is known to people skilled in the industry where a liposome suspension liquid suitable fatty material (for example, stearoyl phosphatidyl ethanolamine, stearoyl phophatidyl chloine, aracadoyl phosphatidyl chloine, and cholesterol) are used as the carrier material.

In the solution or suspension, which contains R848 as its active ingredient and is used for non-oral administration, in the skin, under the skin or for local application, it is possible to include the described here below components. Water used for injections, salt water solution, fixedoil, polyethylene glycol, glycerine, propylene glycol or other synthetic solvents, etc., disinfection dilution agents; benzyl alcohol or methyl paraben etc., disinfection agents; ascorbic acid or sodium sulfonate etc., anti-oxidation agents; ethylene diamine tetra acetate etc., chelating agents; acetate, citric acid or phosphoric acid etc., buffering agents and sodium chloride or dextrose etc., chemicals used for regulating the degree of extension. The non-oral manufactured agents are obtained as they are sealed into ampules, disposable injection vessels, or glass or plastic manufactured repeat administration doses vials. The injection agents can be manufactured according to the usual methods, for example, the above compounds are dissolved in an appropriate solvent (for example, sterile water, buffer solution, physiological salt water solution, etc.) and after that, they are filtered through a filter and sterilized, and then next, they are filled into sterile (non-bacterial) containers. In the case when these are administered inside the vein, the preferred carrier is physiological, salt-water solution or phosphoric acid buffer table salt solution (PBS).

According to the present invention, the external application agent is especially appropriate agent form. Regarding the R848, compared to the imichimode, which has a similar chemical structure, 1-(2-methylpropyl) –1H-imidazo [4, 5-c] chinoline – 4-amine, it has characteristic properties where it is said that its water solubility is at least 20 times higher (at pH 2.5, 5.5 and 7, water solution concentration of at least 1000 micrograms/ml or higher). Because of this property, the drug according to the present invention can be easily manufactured, and not only that, but also, the transfer of the active ingredient towards the center or other structures (anatomical) is low. Also, the effect on the afflicted part is sustainable. As described above, the manufactured agent containing the R848 according to the present invention is a material that is especially excellent as an external application agent.

There are no specific limitations regarding the agent form of the external application agent, and there are the materials that are made into a cream form, paste form, jelly form, gel form, emulsion form, solution form, etc., (soft ointment agent, riniment agent, lotion agent etc.), the materials where the material obtained as the medicine and the skin absorption acceleration agent, are dissolved or mixed and dispersed, is spread over the supporting material (cataplasm, etc.), the materials obtained as the above described medicine and skin absorption acceleration agent (the application in the case of the invention claim 3 of the present invention) are dissolved or mixed and dispersed into an adhesive agent, and this is then spread on the surface of the supporting (carrier) material (plaster agents, tape agents, etc.), etc. As the substrates that are used as the above described substrate agents they are good option as long as they are pharmacologically